Remarks

New Claims

New claims 16 and 17 are drawn to specific embodiments of example 1 at col 7-8. The claims are fully encompassed by the originally presented claims.

Claim 1 recites:

A method for making a cell-matrix construct for use as a heart valve comprising

implanting into an animal **a cell-matrix construct comprising a fibrous matrix in the shape of a heart valve or heart valve leaflet, wherein the matrix is formed of a biocompatible, biodegradable polymer having seeded therein cells** selected from the group consisting of **endothelial cells, myofibroblasts**, skeletal muscle cells, vascular smooth muscle cells, myocytes, fibromyoblasts, and ectodermal cells, wherein the cell-matrix construct can withstand repeated stress and strain.

The new claims are drawn to:

A cell-matrix construct for use as a heart valve or heart valve leaflet comprising

a fibrous polymeric matrix in the shape of a heart valve or heart valve leaflet, wherein the matrix is formed of a **biocompatible, biodegradable polymer having seeded thereon cells comprising myofibroblasts grown to confluence and then endothelial cells seeded thereon.**

There can be no use of the cell matrix other than with the claimed method. Accordingly the new claims are related to the originally presented claims as process of use of product and product and should be examined together. MPEP 806.05(e). This is particularly appropriate in

the case of a reissue application, where withdrawn claims cannot be refiled in a divisional application.

Rejections Under 35 U.S.C. §103

Withdrawal of the previous rejections is greatly appreciated.

Claims 1-5 and 8-15 were rejected under 35 U.S.C § 103 (a) as obvious over U.S. Patent No. 3,514,791 to Sparks ("Sparks") in view of U.S. Patent No. 4,520,821 to Schmidt et al. ("Schmidt"), U.S. Patent No. 5,514,378 to Mikos ("Mikos"), or U.S. Patent No. 5,709,854 to Griffith-Cima et al. ("Griffith-Cima"), and further in view of U.S. Patent No. 4,795,459 or U.S. Patent No. 4,916,193 to Tang, et al.. Applicants respectfully traverse these rejections.

The examiner's statement as to the time of applicant's invention is incorrect. Although this reissue application was filed February 19, 2004, it is based on an application filed **May 19, 1995.**

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of

success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier* , 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the describeing or motivation to combine prior art references." *In re Dembiczak,* 175 F.3d 994 at 999 (Fed. Cir. 1999). While the suggestion to combine may be found in explicit or implicit describeings within the references, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved, the "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *WMS Gaming, Inc. v International Game Technology,* 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular." *In re Dembiczak* , 175 F.3d 994 at 999 (Fed. Cir. 1999). Although with the answer in hand, the "solution" now appears obvious, that is not the test. The references must themselves lead those

in the art to what is claimed.

Analysis

The Claimed Invention

A method for making a cell-matrix construct for use as a heart valve comprising

implanting into an animal

a cell-matrix construct

comprising a fibrous matrix

in the shape of a heart valve or heart valve leaflet,

wherein the matrix is formed of a biocompatible, biodegradable polymer

having seeded therein cells selected from the group consisting of endothelial cells, myofibroblasts, skeletal muscle cells, vascular smooth muscle cells, myocytes, fibromyoblasts, and ectodermal cells,

wherein the cell-matrix construct can withstand repeated stress and strain.

Sparks

Sparks describes a die into which is placed a Dacron mesh secured to a stainless steel supporting ring (see column 5, lines 18-24). The die consists of a tube and mandrel (col. 3, lines 29-31). Figures 6-12 illustrate a die for growing a tricuspid heart valve. As the examiner has noted, Sparks does not disclose a biodegradable polymeric matrix but a metal die in combination with Dacron mesh.

Sparks does not teach or suggest a fibrous matrix formed of a biocompatible, biodegradable polymer and seeded with cells. Sparks relies on natural body processes to produce the necessary connective tissue to fill the die cavity and form the valve graft (see column 2, lines 27-32 and column 5, lines 32-36).

The examiner's attention is drawn to the claim language which requires seeding of a fibrous matrix prior to implantation. Sparks does not disclose forming an implant prior to implantation, but at the time of implantation, nor seeding the implant prior to implantation. As noted at col. 2, lines 6-13, 27-32. see also col. 3, lines 39 to 68.

Attention is also drawn to the structure of the implant described by Sparks. As noted above, the claim is drawn to a fibrous matrix in the shape of a heart valve or heart valve leaflet. This is very clear from the description at col. 5, lines 6-63, and the figures. The implant 60 includes structures such as an outer die member 40, inner die member 42; screws 45, ring 52. In no way can these metal structures be compared to a fibrous mesh, even though a fibrous mesh forms part of the structure. The claims require an implantable material formed entirely of a mesh.

The examiner's statements that the structure of Sparks' would inherently have the claimed properties is without support. It is well known that connective tissue does not share the same ability to withstand repeated stress and strain as the native tissue, which is not connective tissue.

In summary, the differences between the device of Sparks and applicants includes:

A non-degradable metal-Dacron mesh structure, not in the shape of a heart valve, which is implanted and sutured, so connective tissue can grow into the structure

versus

a biodegradable polymeric fibrous mesh in the shape of a heart valve which is seeded with cells prior to implantation.

The differences are significant. First, the structure of Sparks includes structural materials which are used to secure the device and therefore cannot be substituted with a biodegradable

material. If they were, the device would no longer work. Second, Sparks is implanted so that the mesh becomes covered with connective tissue that grows in from the surrounding tissue, not the natural cell types of endothelial cells and myofibroblasts that should form heart leaflets. This results in a difference in structural properties since the properties of connective tissue are clearly quite different from endothelial and myofibroblasts. Third, the shape of the die is not the same and requires removal of the tissue normally surrounding the heart leaflets, unlike with the claimed device. Moreover, one can only wonder how the device of Sparks is secured, since the disclosure repeatedly references attachment to bone (col. 3, lines 62-64), which is of course not present in the heat

Schmidt, Mikos, and Griffith-Cima

The deficiencies in Sparks are not made up for by any of the other cited art.

Mikos discloses preparing biocompatible porous polymer membranes by dispersing salt particles in a biocompatible polymer solution, which are removed following solidification to leave a porous structure, which can be prepared in the form of a particular structure (col. 13, lines 43-52). There is no disclosure of heart valves or leaflets.

Schmidt discloses a bioresorbable mesh or gauze for correcting a defect in a tubular structure such as the ureter, where a single layer of cells is applied to a PLGA mesh, and the mesh implanted to repair the defect..

Griffith-Cima discloses a cell-polymeric solution, which is injected into an animal to form a polymeric hydrogel containing dispersed cells. The method is particularly well suited to formation of a bulking agent, or fill in a hole in a tissue, but cannot be used to form a structure in the shape of a heart valve or leaflet.

Sparks does not disclose a fibrous polymeric matrix in the shape of a heart valve or heart

valve leaflet which is implantable; Sparks discloses a separate die to give fabric a desired structure. None of these references make up for the deficiency in Sparks by teaching or suggesting replacing the die-mandrell-fabric of Sparks with cell-matrix constructs shaped to conform to at least a part of a heart valve or heart leaflet. Therefore, a *prima facie* case of obviousness has not been established, since the references (when combined) do not teach or suggest all the claim limitations.

In addition, there is no motivation to combine these references as the Examiner has done, nor would one skilled in the art have a reasonable expectation of success if one did so, based on the art, to yield a structure which can withstand repeated stress and strain. This is a critical limitation of a claim to a construct which is to be used to replace a heart valve or heart leaflet, structure which must open and close hundreds of times every hour, thousands of times every day, for years.

For example, Sparks describes dies containing **stainless steel, screws,** and **plates** (see column 5, lines 18-31). This is completely different from the formation of tissue by injecting a cell-polymeric **solution** that gels *in vivo* (Griffith-Cima) or preparing biocompatible porous polymer membranes by dispersing particles in a biocompatible polymer **solution** (Mikos). One skilled in the art would not be led by the combination of references to substitute a polymer solution or gel for the stainless steel structure of Sparks.

No where is there any teaching of the need for a cell-matrix structure which can resist repeated stress and strain, much less any teaching of how to achieve one. The advantages of the claimed cell-matrix constructs and methods for manufacture are quite evident from the attached articles. These articles also demonstrate that the resistance to repeated stress and strain is not inherent in the materials.

In summary, Sparks discloses a composite metal-mesh die. The metal die is essential to impart structure to, and secure, the mesh in the form of a heart leaflet. If one combined the die with the degradable polymers of Schmidt, Mikos or Griffith-Cima, the structure would disintigrate, leaving only a piece of useless connective tissue without shape. One skilled in the art would not only have no motivation to combine as the examiner is suggesting, but would have no reasonable expectation of success if he did so.

Jauregui and Tang

The examiner has cited Jauregui and Tang as disclosing the interchangeability of biodegradable and non-degradable materials. First, it should be noted that Sparks does not disclose non-degradable polymeric materials, but metal, which has very different properties and considerations than polymer. Second, as noted above, the non-degradable metal with its specific strength and structural properties is considered to be essential by Sparks.

Jauregui does not disclose a fibrous matrix for seeding of cells. Jauregui discloses a tube onto which a single layer of endothelial cells are seeded. (col. 2, lines 36-59, figure 1). The single reference at col. 8, lines 44-46 does not state that biodegradable and non-degradable polymers are equivalent, merely that both could be used to form a tube. There is nothing with respect to forming a fibrous implant, much less one subjected to the stresses of a heart valve.

Tang discloses a new class of biodegradable polymers useful in a variety of medical applications. There is no disclosure of bioequivalence with non-degradable materials; indeed, the inventors distinguish a number of other materials as being inadequate or not useful.

However, even if Jauregui and Tang taught that one could use biodegradable materials, it would not make up for the differences between what is disclosed by Sparks and what applicants' claim. Sparks describes a device requiring a very strong, non-degradable metal support structure

surrounding a Dacron mesh which is implanted and into which connective tissue grows. In contrast, applicants claim a completely biodegradable polymeric fibrous mesh having cells seeded on it which is implanted and sutured into the implant site, where it has the same structure as the heart leaflet to be replaced. These are simply very different.

Allowance of claims 1-5, and 8-17 is respectfully solicited.

Respectfully submitted,

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